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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,098	03/22/2000	MASAYUKI TSUCHIYA	053466/0274	7563

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,098	TSUCHIYA, MASAYUKI	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-14* is/are pending in the application.

4a) Of the above claim(s) *6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 3-14 are pending.

2. Claims 6-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. Claims 3-5 and 14 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Response to Arguments

5. The rejection of claim 14 and claims 3-5 under 35 U.S.C. 112, second paragraph, for parts b, g, and h in paragraph 6 of the Office Action mailed 9/17/01 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 7/15/03 has been carefully considured but is deemed not to be persuasive. The response states that "artificial amino acid residues" do not occur in nature and the specification on page 12, lines 29-31 define "artificial amino acid sequences" as "those amino acid sequences that cannot be found in nature". In response to this argument, it is still unclear if the phrases mean unnatural amino acids, or mimetics or some other meaning.

The response states that "primary antibody" means a humanized antibody subjected to amino acid substitutions and having biological activity as that of the mouse

antibody and cited page 13, lines 10-19. In response to this argument, in the specification at the cited page the definition states "a FR of the human antibody for use in CDR-grafting is selected...the FR is subjected to amino acid substitution to construct a humanized antibody...in the present invention it is called the primary design antibody". The phrase and definition are indefinite because it is not clear if the mouse antibody is used for the CDRs in the human FR that was selected and then other substitutions are made. In addition in claim 14 recites the "primary design antibody" is humanized and as such is the primary design antibody further humanized?

The response sates that "the homology search for the FR of a primary design antibody" as a search through FR databases for natural FR that maintain the amino acid residue of the primary antibody and is described on page 13, lines 20 to page 14, line 11. In response to this argument, step (4) in claim 14 recites selecting a FR that matches amino acids substituted in step (1) and comprises a sequence that is the same or homologous to the "primary design antibody". It is unclear if the FR chosen is chosen to contain the residues that were originally in the human FR in part (1) or contains the residues that were substituted and as "artificial amino acids". It is still unclear what the homology search obtains.

In addition the response does not address the rejection under 112 second for parts a-c in the previous office action mailed 1/15/03.

6. The rejection of claims 3-5 and claim 14 under 35 U.S.C. 103(a) as being unpatentable over Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4) and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4) is maintained.

The response filed 7/15/03 has been carefully considered but is deemed not to be persuasive. The response states that the methods in the prior art do not result in a FR that is the same as the FR of a human antibody, while maintaining the binding ability to the antigen and the prior art does not result in a fully humanized antibody (see page 3 of response). In response to this argument, the claims do not recite maintaining the binding ability. Also the prior art does result in a fully humanized antibody as defined in the prior art. In addition, Sato et al specifically teach that the FR from the most similar human antibody seemed the best and in the method of Sato et al residues that were altered were those that resulted in residues being more typical in other human FR (see page 375-76) and Sato et al specifically teach the designing of the humanized antibodies based on consensus sequences and homology that will identify any highly irregular sequences or unusual sequences. Moreover, the claims recite replacing residues that are "artificial amino acids" with those that are most homologous or identical to the amino acids that are in the human sequence which the prior art teaches. Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

7. The rejection of claims 3-5 and claim 14 under 35 U.S.C. 103(a) as being unpatentable over Co et al (PNAS 88:2869-2873, 1991, IDS #4) and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4) is maintained.

The response filed The response filed 7/15/03 has been carefully considured but is deemed not to be persuasive. The response states that the methods in the prior art do not result in a FR that is the same as the FR of a human antibody, while maintaining the binding ability to the antigen and the prior art does not result in a fully humanized antibody (see page 3 of response). In response to this argument, the claims do not recite maintaining binding ability. Also the prior art does result in a fully humanized antibody as defined in the prior art. In addition, Co et al teach replacement of residues with consensus residues for the elimination of rare occurrence amino acids in the FR because the amino acids are rare in the human antibodies. Moreover, the claims recite replacing residues that are "artificial amino acids" with those that are most homologous or identical to the amino acids that are in the human sequence which the prior art teaches. Therefore elimination of the unusual amino acids in the FR will further reduce the immunogenicity. Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

8. The rejection of claims 3-5, and 14 under 35 U.S.C. 103(a) as being unpatentable over Roguska et al (Protein Engineering 9:895-904, 1996, IDS #3) and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4) is maintained.

The response filed The response filed 7/15/03 has been carefully considured but is deemed not to be persuasive. The response states that the methods in the prior art do not result in a FR that is the same as the FR of a human antibody, while maintaining the binding ability to the antigen and the prior art does not result in a fully humanized antibody (see page 3 of response). In response to this argument, the claims do not recite maintaining binding ability. Also the prior art does result in a fully humanized antibody as defined in the prior art. In addition, Roguska et al teach a method of humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then replacing residues in the antibody with those found in the human FR (see page 898, left column, GN901v1.1). Moreover, the claims recite replacing residues that are "artificial amino acids" with those that are most homologous or identical to the amino acids that are in the human sequence which the prior art teaches.

It would have been obvious to conduct a homology search using a data base of FR of human antibodies because Roguska et al teach designing based on homology searches of human FR sequences and comparing those residues that are found in the mouse FR with those found at that position in human FR sequences and replacing mouse residues with human to obtain an antibody that are no more likely to be immunogenic that a corresponding CDR-grafted version (see page 901, right column).

Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00

am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER